

[OMIM Home](#) [Search](#) [Comments](#)

## \*249100 MEDITERRANEAN FEVER, FAMILIAL; MEFV

P.D. 1999  
p. 1 - 20 = 20

### *Alternative titles; symbols*

MEF; FMF  
POLYSEROSITIS, RECURRENT  
POLYSEROSITIS, FAMILIAL PAROXYSMAL  
PYRIN, INCLUDED  
MARENOSTRIN, INCLUDED

### TABLE OF CONTENTS

- [DESCRIPTION](#)
- [CLINICAL FEATURES](#)
- [OTHER FEATURES](#)
- [INHERITANCE](#)
- [MAPPING](#)
- [MOLECULAR GENETICS](#)
- [PATHOGENESIS](#)
- [DIAGNOSIS](#)
- [CLINICAL MANAGEMENT](#)
- [POPULATION GENETICS](#)
- [ALLELIC VARIANTS](#)
  - [View List of allelic variants](#)
- [REFERENCES](#)
- [SEE ALSO](#)
- [CONTRIBUTORS](#)
- [CREATION DATE](#)
- [EDIT HISTORY](#)
- [MINI-MIM](#)
- [CLINICAL SYNOPSIS](#)

### Database Links

[MEDLINE](#) [Protein](#) [DNA](#) [Genome](#) [HGMD](#) [Gene Map](#) [GDB](#) [MGD](#)

Gene Map Locus: 16p13

Note: pressing the  symbol will find the citations in MEDLINE whose text most closely matches the text of the preceding OMIM paragraph, using the Entrez MEDLINE neighboring function.

### TEXT

#### DESCRIPTION

Familial Mediterranean fever (FMF) is an autosomal recessive disorder characterized by short, recurrent bouts of fever, accompanied by pain in the abdomen, chest, or joints, and an erysipelas-like rash. Sedimentation rate is increased, but the white count is usually normal. Amyloidosis is a

erythema. Sedimentation rate is increased, but the white count is usually normal. Amyloidosis is a complication and may develop without overt crises of the above description. ☺

## CLINICAL FEATURES

Eshel et al. (1988) suggested that acute, unilateral, short-term orchitis is a feature of FMF; they observed 20 episodes in 13 patients. The natural history, pattern of attacks, and response to colchicine are similar; further, both FMF and Mollaret meningitis are provoked by metaraminol (Barakat et al., 1984). Mollaret (1944) described a syndrome of benign, recurrent meningitis with a characteristic spinal fluid picture: pleocytosis of mixed cellular type including endothelial cells (Mollaret cells) during the attack, in the absence of any positive agent. These attacks were separated by symptom-free periods lasting from days to years. Recovery was complete, with no neurologic deficit. Barakat et al. (1988) concluded that Mollaret meningitis is a feature of FMF. Schwabe and Monroe (1988) described a 32-year-old non-Ashkenazi Jewish man in whom meningitis first developed in Morocco at the age of 1 year. Between the ages of 26 and 31 years, he had 6 attacks of fever, frontal headache, nausea, and stiff neck, with positive Kernig and Brudzinski signs. ☺

Armenian (1983) compared the characteristics of 79 patients seen for the first time in a special clinic for FMF in its first 16 months of operation, with the characteristics of 79 patients who presented during the last 6 years of its operation. The patients studied during the first period had a more severe form of the disease with multiple clinical manifestations such as proteinuria and amyloidosis. There were more males and more patients with a positive family history in the earlier group. Armenian (1983) emphasized the importance of a population base and 'enrollment bias'--differences in referral pattern, in case selection, and in the sources of data--in accounting for significant variation in the frequency of various clinical manifestations in published series of FMF cases. ☺

Ozyilkan et al. (1994) suggested that bronchial asthma is abnormally infrequent in FMF patients. This was the case not only in patients on colchicine because an absence of a history of asthma before the diagnosis of FMF was also found.

In a study of FMF in Kuwait, Barakat et al. (1986) reported on an 11-year experience with 175 Arab patients. Amyloidosis was rare. In Saudi Arabia, Majeed and Barakat (1989) found that 48 of 88 affected children had onset before the age of 5 years. In a 60-year-old Arab man with FMF, Agmon et al. (1984) observed selective amyloid involvement of the zona glomerulosa of the adrenal cortex resulting in isolated hypoaldosteronism. As a rule the glomerulosa is spared in adrenal amyloidosis of FMF. Knecht et al. (1985) found abnormally high levels of serum amyloid A in attack-free intervals and very high levels at the onset of attacks. Although there is a striking difference in the frequency of amyloid nephropathy in different ethnic groups, the elevation of SAA (serum amyloid A; 104750) during and between attacks is the same, and interethnic marriages produce affected progeny (Pras et al., 1982). ☺

Rawashdeh and Majeed (1996) reviewed findings from the FMF pediatric patient population in northern Jordan (all children were of Jordanian, Palestinian, or Syrian origin). The 192 patients first presented between the ages of 4 months and 16 years. The mean delay in diagnosis was 3.7 years and was increased for children who presented before the age of 2 years. Abdominal pain was the most common presenting symptom and occurred in 51%, while arthritis and pleuritis occurred 26% and 23% respectively as presenting symptoms. The investigators noted that family history was positive in 62% of the children, which was not surprising in this autosomal recessive disorder, given the 64% consanguinity rate in northern Jordan. Minimum prevalence was given as 1 in 2600 with an estimated gene frequency in the childhood population of 1 in 50 (calculated on the numbers of diagnosed patients). The authors warned that the frequency of FMF among Jordanian Arab children was greater than previously estimated. ☺

In Ankara, Turkey, Saatci et al. (1997) analyzed 425 FMF patients without and 180 with amyloidosis. Of the latter group 103 had amyloidosis type I and 57 had amyloidosis type II. (Type I amyloidosis was defined as amyloidosis developing subsequent to clinical features of FMF, whereas type II was defined as amyloidosis developing as the initial manifestation.) The male-to-female ratio was higher in the amyloidosis population (111 to 69) than it was in the FMF population without amyloidosis (225 to 200) ( $P = 0.048$ ). The consanguinity rate was the same in the 2 groups. A family history of amyloidosis was significantly more frequent in the amyloidosis group ( $P = 0.0001$ ). The combination of positive family history of amyloidosis and consanguinity increased the risk of amyloidosis more than 6 fold. The 5-year chronic renal failure free survival was 43.1% and 18.7% in type I and type II amyloidosis, respectively. Saatci et al. (1997) found 10 cases of Henoch-Schonlein purpura and 9 of polyarteritis nodosa among their patients. The significance of the association between FMF and vasculitis was unclear. Among 435 FMF patients treated with colchicine, only 10 (2.3%) developed amyloidosis, thus confirming that this drug protects patients from the complication. ☈

In a retrospective study of 4,000 FMF patients, using a computer chart review, Kees et al. (1997) found that over a period of 20 years, 1 or more episodes of pericarditis were recorded in 27 patients. Each patient experienced 1 to 3 pericarditis attacks, lasting a mean of 4.2 days, accompanied by elevated temperature and symptoms of FMF attack at another site. The pericarditis resolved spontaneously and left no sequelae. ☈

Pras et al. (1998) compared the clinical features of FMF in North African Jews and Iraqi Jews, the 2 largest population groups suffering from the disease in Israel. North African Jews were found to have more severe disease manifested by earlier age of onset, increase in frequency and severity of joint involvement, higher incidence of erysipelas-like erythema, and higher dose of colchicine required to control symptoms. ☈

#### OTHER FEATURES

Schwabe and Lehman (1984) reviewed the search for the basic defect in this disorder. Normal peritoneal fluid contains an inhibitor of neutrophil chemotaxis that acts by antagonizing the component-derived chemotactic anaphylatoxin C5a (113995). The inhibitor resembles a substance found in synovial fluids and is a protein with molecular weight 40,000. Matzner and Brzezinski (1984) found that this inhibitory activity was less than 10% of normal in peritoneal fluid from FMF patients. Inadequate suppression of the inflammatory response to C5a that is released accidentally may be responsible for the inappropriate inflammatory reactions of FMF. Colchicine may prevent attacks by suppressing neutrophil motility and blocking their mobilization to sites of C5a release. Matzner et al. (1984) found a decrease of the C5a inhibitory activity in synovial fluid from patients with FMF. Patients with other forms of inflammatory arthritis and osteoarthritis had normal levels. Ayesh et al. (1990) further characterized the 40-kD inhibitor protein and showed that it is a serine protease. Documentation of a carrier state of reduced C5a-inhibitor activity in unaffected obligatory heterozygotes such as parents or offspring would help establish the inhibitor as the site of the primary defect. The patients studied by Matzner and Brzezinski (1984) were Sephardim; comparable studies in Armenians with FMF will be of interest because of the much lower frequency of amyloidosis with FMF in this ethnic group (Schwabe and Peters, 1974). ☈

#### INHERITANCE

Shohat et al. (1992) found concordance for FMF in all 10 monozygotic twin pairs and only 3 of 11 dizygotic twin pairs. However, variability in the clinical manifestations and degree of severity were

noted within twin pairs, supporting the contention that the lower than expected incidence of FMF observed in segregation analysis is due to genetically affected but clinically undiagnosed patients. ☺

Under the term periodic peritonitis, Reimann et al. (1954) described many cases from Lebanon, most of them Armenian. In 1 remarkable family, survivors of the siege of Musa Dagh, 20 affected persons occurred in 5 generations. There were 3 instances of skips in the pedigree. Conceivably, high gene frequency and small breeding group can account for the findings as representing pseudodominant inheritance. In Turkey, many cases of FMF are observed in persons without known Armenian ancestry (Sokmen, 1959). This condition was called 'familial paroxysmal polyserositis' by Siegal (1964), who was the first to delineate the disorder clearly in the United States and who observed rather numerous cases in Ashkenazim. Barakat et al. (1984) referred to FMF as 'recurrent hereditary polyserositis.' ☺

Rogers et al. (1989) presented evidence corroborating the autosomal recessive inheritance of FMF in Armenians. Using extended pedigree data, they calculated an FMF gene frequency of 0.073 and a carrier rate of 1 in 7, which is about 4 times the frequency in non-Ashkenazi Jews. Four of 64 families had 1 parent affected as well as the proband; the high gene frequency can explain this phenomenon. The male/female ratio of 1.7 found in non-Ashkenazi Jews indicates reduced penetrance in females and probably also obtains in Armenians. ☺

Yuval et al. (1995) found 77 families, with 240 FMF patients, in which the disorder affected more than one generation. In 75 of these families, the occurrence of FMF in more than one generation was found to be consistent with a recessive mode of inheritance due to a high gene frequency and consanguinity of the parents. In 2 families, however, one of Ashkenazi and the other of Georgian Iraqi origin, in which FMF occurred in 4 consecutive generations, the transmission could be explained only by autosomal dominant inheritance. Whether the disorder in this family is due to mutation at a separate locus or represents a variant allele at the FMF locus on chromosome 16 will be answered by molecular genetic studies. ☺

## MAPPING

In linkage studies in Armenians, Shohat et al. (1990) excluded FMF from those portions of the genome at least 15 cM from 14 genetic markers, and in other linkage studies, Shohat et al. (1990) concluded that the immunogenetic region of chromosome 6 could be excluded from linkage with FMF in Armenian families. By linkage analysis, Gruberg et al. (1991) excluded several candidate genes including lipocortins, dopamine beta-hydroxylase, and interleukins 1 and 6. Kastner et al. (1991) presented a 90-marker exclusion map. With marker D17S74 on chromosome 17, they obtained a maximum multipoint lod score of 3.54 approximately 15 cM telomeric to the marker. ☺

Pras et al. (1992) succeeded in mapping the FMF gene to 16p by linkage studies in 27 non-Ashkenazi Jewish families in Israel. One DNA marker, D16S84, gave a maximum lod score of 9.17 at a recombination frequency of 0.04. A probe associated with the hemoglobin alpha complex (5-prime-HVR) gave a maximal lod score of 14.47 at theta = 0.06. Multipoint analysis indicated that the likely order is as follows: cen--FMF--D16S84--HBA--tel. The maximal multipoint lod score was 19.86. There was a striking degree of homozygosity at chromosome 16p loci in the affected offspring of 8 consanguineous couples, thus supporting linkage by the method of homozygosity mapping. Pras et al. (1992) and Fischel-Ghodsian et al. (1992) found that the FMF gene maps to 16p in all ethnic groups, including Armenians and Ashkenazi and non-Ashkenazi Jews. ☺

Studying 14 Armenian and 9 non-Ashkenazi Jewish families with FMF, Shohat et al. (1992) found linkage to the alpha-globin complex on 16p in both groups, with no evidence for genetic heterogeneity either between the groups or within the groups. Aksentijevich et al. (1992, 1993) observed different haplotypes associated with the disease in strong linkage disequilibrium in Moroccan and Iraqi Jewish

haplotypes associated with the disease in strong linkage disequilibrium in Moroccan and Iraqi Jewish families. This, together with the fact that Moroccans had a much more severe form of FMF, suggested that the 2 groups carry different allelic mutations. The mutation in Armenians may also be different from that in Moroccans, accounting for the milder phenotype. ☺

Aksentijevich et al. (1993) attempted more precise mapping of MEF by the homozygosity method for 8 of 9 markers. The rate of homozygosity among 26 affected inbred individuals was higher than that among their 20 unaffected sibs. Localizing MEF more precisely on the basis of homozygosity rates alone would be difficult, they concluded, for 2 reasons: the high FMF carrier frequency increases the chance that inbred offspring have the disease without being homozygous by descent at the MEF locus; and several of the markers in the MEF region are relatively nonpolymorphic, with a high rate of homozygosity, regardless of their chromosomal location. ☺

Aksentijevich et al. (1993) reexamined the linkage data to ascertain the possible reason for the earlier conclusion that the gene causing FMF is on 17q (Kastner et al., 1991). They found that the data with the chromosome 17 markers alone suggested locus heterogeneity. Nonetheless, the families were not separable into complementary subgroups showing linkage either to chromosome 16 or to chromosome 17. They examined the possibility that the positive lod score for chromosome 17 might reflect a secondary, modifying locus. However, by several measures of disease severity, families with positive lod scores for chromosome 17 loci had no worse disease than those with negative lod scores for these loci. They concluded that chromosome 17 does not carry a major FMF susceptibility gene for some families and does not encode a disease-modifying gene. Rather, it appeared that linkage to chromosome 17 was a 'false positive' (type I) error. These results reemphasize the fact that a lod score of 3.0 corresponds to a posterior probability of linkage of 95%, with an attendant 1 in 20 chance of observing a false positive. FMF in the Arab population is said to be characterized by a low incidence of arthritis, amyloidosis, and erysipeloid erythema. These differences in disease expression raise the possibility of locus heterogeneity. However, Pras et al. (1994) found that the FMF gene maps to 16p in Druze and Moslem Arab families. Shohat et al. (1992) had shown that the gene maps to the same region in Armenians and non-Ashkenazi Jews. ☺

Using linkage disequilibrium mapping in the study of 65 Jewish, Armenian, and Arab families, Levy et al. (1996) obtained a maximal lod score of 49.2 at a location 1.6 cM centromeric to D16S246. A specific haplotype using 3 markers was found in 76% of Moroccan and 32% of non-Moroccan Jewish carrier chromosomes, but this haplotype was not overrepresented in Armenian or Arab FMF carriers. Since the Moroccan Jewish community represents a relatively recently established and genetically isolated founder population, Levy et al. (1996) analyzed the Moroccan linkage-disequilibrium data and placed the FMF susceptibility gene within 0.305 cM of D16S246. ☺

The French FMF Consortium (1996) narrowed the location of the FMF gene to a 250-kb interval through the study of non-Ashkenazi Jewish founder haplotypes accomplished by use of 15 microsatellite markers. They concluded that the FMF locus is situated between D16S3070 and D16S3275. Sood et al. (1997) used a high-resolution clone map of the 16p13.3 region to narrow the FMF interval. They identified several founder haplotypes in various ethnic groups. ☺

Akarsu et al. (1997) studied 8 consanguineous Turkish families with at least 2 offspring affected with FMF. In 6 of these families, linkage was observed with a maximum lod score of 9.115 at theta = 0.00 for marker D16S3024. Two families, however, were unlinked to this region. Haplotype construction showed homozygosity for the region bounded by D16S3070 and D16S2617 in 5 families; 80% allelic association was shown with D16S2617. ☺

#### MOLECULAR GENETICS

### Phenotype/Genotype

Sack (1988) found novel structural changes in members of the serum amyloid A gene family in 4 FMF patients of varied ethnic backgrounds. He interpreted these observations as suggesting 'that alterations of serum amyloid A genes, their protein products, and/or their regulation may be responsible' for FMF. Shohat et al. (1989, 1990) and Sack et al. (1991) excluded close linkage between FMF and the SAA locus (104750), however. Similarly, Shohat et al. (1989, 1990) demonstrated that the gene for serum amyloid P component (104770) is not closely linked to the locus for FMF. The complication of amyloidosis varies in frequency among various ethnic groups. Although FMF might not be 'caused' primarily by a mutation in the SAA or SAP gene, proneness to amyloidosis might differ according to particular polymorphic allele at one or the other locus carried by the ethnic group. The failure of Shohat et al. (1989, 1990) to find an association of a particular polymorphism with amyloidosis probably rules out this possibility. Shohat et al. (1989) advanced the hypothesis that FMF patients are homozygous for a mutant allele for one of the lipocortin genes (151690), resulting in either lipocortin deficiency or production of an abnormal lipocortin protein. Lipocortin may be especially critical during stress. Its deficiency could result in a lack of feedback inhibition and an increase in the release of arachidonic acid, precursor of the potent mediators of inflammation. The deficiency might result in increased generation of prostaglandins, leukotrienes, and other inflammatory mediators by granulocytes, which then further activate phospholipase A2 by a feedback mechanism.

The International FMF Consortium (1997) cloned a gene from a 115-kb FMF candidate interval on 16p and identified 3 disease-related mutations. Haplotype and mutational analyses showed ancestral relationships among carrier chromosomes that have been separated for centuries. The novel gene encodes a 3.7-kb transcript that is expressed almost exclusively in mature granulocytes. The predicted 781-amino acid protein, which they termed pyrin, is a member of a family of nuclear factors homologous to the Ro52 antigen (109092). The investigators commented that the discovery of this gene should shed light on the regulation of the acute inflammatory response. None of the mutations that they identified result in a truncated protein, and the periodic nature of inflammatory attacks in FMF is consistent with a protein that functions adequately at steady state but decompensates under stress. With identification of the mutant protein, it may be easier to recognize environmental triggers that lead to attacks. The International FMF Consortium (1997) suggested that phenotypic differences may be related to different mutations. The met694-to-val mutation (249100.0001) is frequent in populations with a higher incidence of systemic amyloidosis, whereas the val726-to-ala mutation (249100.0003) was found in a population in which amyloidosis is less common. They also suggested that a heterozygous selective advantage based on heightened inflammatory response to some pathogen or class of pathogens endemic in the Mediterranean may be responsible for the high frequency of the MEFV gene in populations of that geographic extraction.

Simultaneously and independently, the French FMF Consortium (1997) identified transcriptional units in a critical MEFV interval of 60 kb on the basis of genomic sequence analysis and exon trapping. Four genes were identified: one encoding an olfactory receptor (603232), one encoding a protein with similarities to zinc finger proteins (603231), one represented by expressed sequence tags (ESTs), and one encoding a protein the investigators named marenostin (from the Latin name of the Mediterranean Sea, mare nostrum). The partial predicted amino acid sequence is related to butyrophilin (601610). That marenostin is the FMF disease gene was demonstrated by the finding of 4 sequence variations (e.g., 249100.0001) that correlated with disease in various ethnic groups. In 72% of the patients in their sample, 1 or 2 of the 4 mutations were found.

### PATHOGENESIS

Babior and Matzner (1997) suggested that the pathogenesis of FMF is as follows: pyrin, or

marenostrin, is postulated to activate the biosynthesis of a chemotactic-factor inactivator, an enzyme that normally occurs in the serosal fluids. They suggested that a chemotactic factor (probably C5a; 113995) can be released by subclinical injury to the serosa during normal activities, but the amounts released are small enough that they are cleared by the inactivating enzyme before they can provoke an inflammatory reaction. In FMF the inactivating enzyme is absent, allowing the chemotactic factors to survive long enough to call in neutrophils, which then release a variety of products, including an enzyme that generates more C5a. The result is an upward spiral that culminates in a full-blown inflammatory reaction: an attack of FMF. ☺

## DIAGNOSIS

By means of a placebo-controlled, double-blind, crossover study, Barakat et al. (1984) demonstrated that intravenous infusion of 10 mg of metaraminol bitartrate ("Aramine") in 500 ml normal saline over a period of 3 to 4 hrs was followed by a typical attack of FMF in all of 21 persons with the disease and in none of 21 control subjects. The induced attacks were milder and of shorter duration than the spontaneous ones. The metaraminol-induced attacks could be prevented with colchicine. In connection with the metaraminol provocative test for the diagnosis of FMF (Cattan et al., 1984), Barakat et al. (1984) suggested that abdominal tenderness should be included as a feature indicating positive test. ☺

Fischel-Ghodsian et al. (1993) identified 2 flanking markers and microsatellite markers that allow preclinical diagnosis in most pedigrees with affected persons.

Dupont et al. (1997) proposed the use of a set of 7 microsatellite markers for diagnosis and heterozygote analysis: D16S283 and D16S3124, telomeric of the FMF disease gene; D16S3070, D16S3082, and D16S3275, which showed no recombination with disease; and D16S2622 and D16S3027, centromeric of the FMF locus. They found this set of markers to be informative in 100% of previously diagnosed non-Ashkenazi Jewish patients. In addition, 73% of patients from this population were homozygous for the 3-3-9 or 3-3-18 haplotype at D16S3070, D16S3082, and D16S3275. Dupont et al. (1997) suggested that these markers could be used for diagnosis of sporadic cases in this population, although absence of homozygosity would not exclude the diagnosis. ☺

## CLINICAL MANAGEMENT

Schwabe and Nishizawa (1987) described a 36-year-old male of pure Japanese ancestry with a classic 20-year history of recurrent FMF manifested by self-limited attacks of fever plus pleuritis, peritonitis, or arthritis. The attacks were completely suppressed by daily prophylactic colchicine but recurred when the drug was briefly discontinued. He had been free of attacks for 10 years while taking 1.2 mg of colchicine daily. ☺

Goldfinger (1972), Wolff et al. (1974), and Ravid et al. (1977) reported benefit from colchicine in reducing painful attacks in FMF. Zemer et al. (1986) presented evidence that colchicine prevents and ameliorates amyloidosis in FMF. They followed 1,070 patients with FMF for 4 to 11 years after they were advised to take colchicine to prevent febrile attacks. Overall, at the end of the study, the prevalence of nephropathy was one-third of that in a study conducted before colchicine was used to treat FMF. Among 960 patients who initially had no evidence of amyloidosis, proteinuria appeared in 4 who adhered to a prophylactic schedule and in 16 of 54 who admitted noncompliance. Life-table analysis showed that the cumulative rate of proteinuria was 1.7% after 11 years in the compliant patients and 48.9% after 9 years in the noncompliant patients. All 24 patients with nephrosis or uremia had progressive deterioration of renal function. In 86 patients with proteinuria but no nephrotic syndrome, proteinuria resolved in 5 and stabilized in 68 (for more than 8 years in 40 patients). In the

experience of Knecht et al. (1985), patients in whom colchicine fails to prevent attacks and SAA spikes enjoy as effective protection against renal amyloidosis as do colchicine-responsive patients. Jones et al. (1977) reported recurrence of amyloid in a grafted kidney. Zemer et al. (1993) reported a family in which 6 of 9 sibs had FMF, the oldest born in 1950 and the youngest in 1970. The youngest was brought for clinical examination at the age of 12 years by his 'painfully experienced and observant mother' because his urine looked suspicious, and proteinuria was found. With continuous colchicine treatment, proteinuria persisted for 3 years and then gradually subsided over the next 2 years. By the age of 22 years, his urine had been free of protein for 5 years. ☺

Ben-Chetrit et al. (1996) measured simultaneous colchicine levels in serum and breast milk in 4 breast-feeding women with a diagnosis of FMF for over 7 years. The authors found that the levels of colchicine in serum and breast milk paralleled each other. The peak concentration of colchicine occurred between 1 to 3 hours in all women. They found no abnormalities in the 4 children after 10 months of follow-up. Although the authors postulated that colchicine did 'no harm to the breast feeding infant,' they also stated that some women may consider breastfeeding 12 hours after the colchicine has been ingested and bottle feed for the other 12 hours. ☺

## POPULATION GENETICS

This disease occurs mainly in Armenians and Sephardic Jews (those who left Spain during the Inquisition and settled in various countries bordering the Mediterranean). The possibility that the disorder in Armenians is distinct from that in Sephardic Jews is suggested by the lower frequency of amyloidosis (Schwabe and Peters, 1974) and longer average survival. ☺

Sohar et al. (1967) estimated that in some Jewish groups the phenotype frequency is 1 in 2,720 and that the minimal estimates for gene frequency and heterozygote frequency are 1 in 52 and 1 in 26, respectively. The number of Ashkenazi cases observed in Israel by Sohar et al. (1967) is sufficient to make it not surprising that a fair number of cases are observed in the large Ashkenazi group in the United States. Schwabe et al. (1977) reported 197 patients: 131 Armenians, 11 Ashkenazim, 27 non-Ashkenazi Jews, and 28 others. In an analysis of 1,327 cases from the literature, Meyerhoff (1978) found that 50% were Sephardic, 22% Armenian, 11% Arabian, 7% Turkish, and 5% Ashkenazi. Rawashdeh and Majeed (1996) reviewed the incidence of amyloidosis complicating FMF among several Mediterranean ethnic groups. ☺

Using extended pedigree data of 90 FMF probands, Daniels et al. (1995) calculated the FMF gene frequency in various ethnic groups in Israel by analyzing the frequency in a total of 2,312 first cousins. The heterozygote frequencies were as follows: 1 in 4.9 (0.2 +/- 0.06) for the Libyan subgroup; 1 in 6.4 (0.16 +/- 0.03) for the subgroup from other North African countries; 1 in 13.3 (0.07 +/- 0.04) for the Iraqi subgroup; 1 in 11.4 (0.09 +/- 0.06) for the Ashkenazic subgroup; and 1 in 29.4 (0.03 +/- 0.03) for the remaining ethnic groups. The observed number of affected parents and affected offspring of probands was in agreement with the estimated gene frequency. Pras et al. (1998) commented that North African Jews and Iraqi Jews were the 2 largest population groups suffering from FMF in Israel. North African Jews were found to have more severe disease manifested by earlier age of onset, increase in frequency and severity of joint involvement, higher incidence of erysipelas-like erythema, and higher dose of colchicine required to control symptoms. ☺

Chen et al. (1998) found that of 34 disease alleles in FMF patients of Turkish origin, 19 carried the met694-to-val mutation (249100.0001) and 5 each carried the met680-to-ile (249100.0004) and the val726-to-alanine (249100.0003) mutations. The mutation was not identified in 5 of the 34 alleles. ☺

Each of the 4 mutations that were first identified as the basis for FMF segregates with 1 ancestral

haplotype; these 4 mutations, all clustered in exon 10, are met694-to-val (249100.0001), met694 to ile (249100.0002), val726 to ala (249100.0003), and met680 to val (249100.0004). In a search for additional MEFV mutations in 120 apparently nonfounder FMF chromosomes, Bernot et al. (1998) observed 8 novel mutations in exon 2 (E148Q, E167D, and T267I), exon 5 (F479L), and exon 10 (I692del, K695R, A744S, and R761H). Except for E148Q and K695R, all mutations were found in a single chromosome. Mutation E148Q was found in all ethnic groups studied and in association with a novel ancestral haplotype in non-Ashkenazi Jews. Altogether, these new findings definitively established the marenostrin/pyrin-encoding gene as the MEFV locus responsible for FMF. ☺

## ALLELIC VARIANTS

### .0001 FAMILIAL MEDITERRANEAN FEVER [MEFV, MET694VAL]

The International FMF Consortium (1997) found a met694-to-val (M694V) mutation of the pyrin gene in a large number of affected individuals bearing 4 apparently distinct haplotypes. The mutation was defined as a 2080A-G transition.

The French FMF Consortium (1997) identified this A-to-G transition in the MEFV gene at nucleotide 1170 of their partial cDNA sequence. They referred to the mutation as the 'MED' variation because it was observed in affected members of families of various origins (Jewish, Armenian, Turkish, Arabian) sharing the MED haplotype. The ethnic diversity indicated that the mutation is ancient and confirms founder effect in the origin of a large fraction of FMF cases in the Mediterranean basin. ☺

The MED mutation is found in about 80% of the FMF Jewish (Iraqi and North African) chromosomes. To see if the presence of this mutation could be correlated with particular traits of the disease, Dewalle et al. (1998) examined clinical features in a panel of 109 Jewish FMF patients with 0, 1, or 2 MED mutations. They showed that homozygosity for this mutation was significantly associated with a more severe form of the disease. In homozygous patients, the disease started earlier (mean age 6.4 vs 13.6) and both arthritis and pleuritis were twice as frequent as in patients with one or no M694V mutation. Moreover, all 3 of 3 patients with amyloidosis displayed 2 MED mutations. No association was found with fever, peritonitis, response to colchicine, and erysipeloid eruption. ☺

### .0002 FAMILIAL MEDITERRANEAN FEVER [MEFV, MET694ILE]

In an Arabian family, the French FMF Consortium (1997) found that affected members bearing an ARA2 haplotype had a G-to-A transition of nucleotide 1172 of their partial cDNA sequence that converted ATG (met) to ATA (ile) in the marenostrin protein. The mutation results in a met694-to-ile amino acid change in the full-length polypeptide. ☺

### .0003 FAMILIAL MEDITERRANEAN FEVER [MEFV, VAL726ALA]

The International FMF Consortium (1997) found this mutation of the pyrin gene in a Druze family and in other FMF patients and carriers with the Druze (D) haplotype. They characterized the mutation as a 2177T-C transition, resulting in a val726-to-alanine amino acid substitution in the protein. In FMF patients with the D haplotype and in patients with an ARM3 haplotype, the French FMF Consortium (1997) likewise found this T-to-C transition, at nucleotide 1267 of their partial cDNA sequence. ☺

### .0004 FAMILIAL MEDITERRANEAN FEVER [MEFV, MET680ILE]

In the affected offspring of a single Armenian family, the International FMF Consortium (1997) found homozygosity for a 2040G-C transversion that resulted in a met680-to-ile amino acid substitution in

the pyrin protein. In Turkish and Armenian FMF patients with the RM2 haplotype, the French FMF Consortium (1997) likewise found this G-to-C transversion at nucleotide 1130 of their partial cDNA sequence of the MEFV gene. ☺

.0005 FAMILIAL MEDITERRANEAN FEVER [MEFV, GLU148GLN]

See Bernot et al. (1998).

.0006 FAMILIAL MEDITERRANEAN FEVER [MEFV, GLU167ASP]

See Bernot et al. (1998).

.0007 FAMILIAL MEDITERRANEAN FEVER [MEFV, THR267ILE]

See Bernot et al. (1998).

.0008 FAMILIAL MEDITERRANEAN FEVER [MEFV, PHE479LEU]

See Bernot et al. (1998).

.0009 FAMILIAL MEDITERRANEAN FEVER [MEFV, ILE692DEL]

See Bernot et al. (1998).

.0010 FAMILIAL MEDITERRANEAN FEVER [MEFV, LYS695ARG]

See Bernot et al. (1998).

.0011 FAMILIAL MEDITERRANEAN FEVER [MEFV, ALA744SER]

See Bernot et al. (1998).

.0012 FAMILIAL MEDITERRANEAN FEVER [MEFV, ARG761HIS]

See Bernot et al. (1998).

## SEE ALSO

Aksentijevich et al. (1993) ; Armenian and Khachadurian (1973) ; Barakat et al. (1984) ; Benson et al. (1977) ; Dinarello et al. (1974) ; Dormer and Hale (1962) ; Ehrenfeld et al. (1961) ; Flatau et al. (1982) ; Heller et al. (1961) ; Hurwicz et al. (1970) ; Ilfeld and Kuperman (1982) ; Janeway and Mosenthal (1908) ; Khachadurian and Armenian (1974) ; Lawrence and Mellinkoff (1959) ; Ludomirsky et al. (1981) ; Meyerhoff (1980) ; Ozdemir and Sokmen (1969) ; Pras et al. (1992) ; Reich and Franklin (1970) ; Rubinger et al. (1979) ; Schlesinger et al. (1984) ; Shohat et al. (1989) ; Shohat et al. (1989) ; Shohat et al. (1992) ; Shohat et al. (1990) ; Shohat et al. (1990) ; Siegal (1945) ; Zemer et al. (1974)

## REFERENCES

1. Agmon, D.; Green, J.; Platau, E.; Better, O. S. :  
Isolated adrenal mineralocorticoid deficiency due to amyloidosis associated with familial

**Mediterranean fever** *Im. J. Med. Sci.* 288: 40-43, 1984.  
PubMed ID : [6465194](#)

2. Akarsu, A. N.; Saatci, U.; Ozen, S.; Bakkaloglu, A.; Besbas, N.; Sarfarazi, M. :  
**Genetic linkage study of familial Mediterranean fever (FMF) to 16p13.3 and evidence for genetic heterogeneity in the Turkish population.** *J. Med. Genet.* 34: 573-578, 1997.  
PubMed ID : [9222966](#)
3. Aksentijevich, I.; Gruberg, L.; Pras, E.; Balow, J. E., Jr.; Kovo, M.; Gazit, E.; Dean, M.; Pras, M.; Kastner, D. L. :  
**Evidence for linkage of the gene causing familial Mediterranean fever to chromosome 17q in non-Ashkenazi Jewish families: second locus or type I error?** *Hum. Genet.* 91: 527-534, 1993.  
PubMed ID : [8340105](#)
4. Aksentijevich, I.; Pras, E.; Grubberg, L.; Shen, Y.; Holman, K.; Helling, S.; Prosen, L.; Sutherland, G. R.; Richards, R. I.; Ramsburg, M.; Dean, M.; Pras, M.; Amos, C. I.; Kastner, D. L. :  
**Refined mapping of the gene causing familial Mediterranean fever, by linkage and homozygosity studies.** *Am. J. Hum. Genet.* 53: 451-461, 1993.  
PubMed ID : [8328461](#)
5. Aksentijevich, I.; Pras, E.; Grubberg, L.; Shen, Y.; Richards, R. I.; Prosen, L.; Helling, S.; Pras, M.; Kastner, D. L. :  
**Linkage disequilibrium in the familial Mediterranean fever candidate region. (Abstract)** *Am. J. Hum. Genet.* 51 (suppl.): A181, 1992.
6. Armenian, H. K. :  
**Enrollment bias and variation in clinical manifestations: a review of consecutive cases of familial paroxysmal polyserositis.** *J. Chronic Dis.* 36: 209-212, 1983.  
PubMed ID : [6822630](#)
7. Armenian, H. K.; Khachadurian, A. K. :  
**Familial paroxysmal polyserositis: clinical and laboratory findings in 120 cases.** *Leban. Med. J.* 26: 605-614, 1973.
8. Ayesh, S. K.; Ferne, M.; Flechner, I.; Babior, B. M.; Matzner, Y. :  
**Partial characterization of a C5a-inhibitor in peritoneal fluid.** *J. Immun.* 144: 3066-3070, 1990.  
PubMed ID : [2324495](#)
9. Babior, B. M.; Matzner, Y. :  
**The familial Mediterranean fever gene—cloned at last.** *New Eng. J. Med.* 337: 1548-1549, 1997.  
PubMed ID : [9366590](#)
10. Barakat, M. H.; El-Khawad, A. O.; Gumaa, K. A.; El-Sobki, N. I.; Fenech, F. F. :  
**Metaraminol provocative test: a specific diagnostic test for familial Mediterranean fever.** *Lancet* I: 656-657, 1984.  
PubMed ID : [6142351](#)
11. Barakat, M. H.; El-Sobki, N. I.; El-Khawad, A. O.; Gumma, K. A.; Fenech, F. F. :  
**Diagnosing familial Mediterranean fever. (Letter)** *Lancet* II: 41-42, 1984.  
PubMed ID : [6145957](#)
12. Barakat, M. H.; Karnik, A. M.; Majed, H. W. A.; El-Sobki, N. I.; Fenech, F. F. :  
**Familial Mediterranean fever (recurrent hereditary polyserositis) in Arabs--a study of 175**

- patients and review of the literature. *Quart. J. Med.* 60: 837-86, 1986.
13. Barakat, M. H.; Mustafa, H. T.; Shakir, R. A. :  
**Mollaret's meningitis: a variant of recurrent hereditary polyserositis, both provoked by metaraminol.** *Arch. Neurol.* 45: 926-927, 1988.  
PubMed ID : [3395269](#)
14. Ben-Chetrit, E.; Scherrmann, J.-M.; Levy, M. :  
**Colchicine in breast milk of patients with familial Mediterranean fever.** *Arthritis Rheum.* 39: 1213-1217, 1996.  
PubMed ID : [8670333](#)
15. Benson, M. D.; Skinner, M.; Cohen, A. S. :  
**Amyloid deposition in a renal transplant in familial Mediterranean fever.** *Ann. Intern. Med.* 87: 31-34, 1977.  
PubMed ID : [327890](#)
16. Bernot, A.; da Silva, C.; Petit, J.-L.; Cruaud, C.; Caloustian, C.; Castet, V.; Ahmed-Arab, M.; Dross, C.; Dupont, M.; Cattan, D.; Smaoui, N.; Dode, C.; Pecheux, C.; Nedelec, B.; Medaxian, J.; Rozenbaum, M.; Rosner, I.; Delpech, M.; Grateau, G.; Demaille, J.; Weissenbach, J.; Touitou, I. :  
**Non-founder mutations in the MEFV gene establish this gene as the cause of familial Mediterranean fever (FMF).** *Hum. Molec. Genet.* 7: 1317-1325, 1998.  
PubMed ID : [9668175](#)
17. Cattan, D.; Dervichian, M.; Courillon, A.; Nurit, Y. :  
**Metaraminol provocation test for familial Mediterranean fever.** (Letter) *Lancet* I: 1130-1131, 1984.  
PubMed ID : [6144866](#)
18. Chen, X.; Fischel-Ghodsian, N.; Cersek, A.; Hamon, M.; Ogur, G.; Lotan, R.; Danon, Y.; Shohat, M. :  
**Assessment of pyrin gene mutations in Turks with familial Mediterranean fever (FMF).** *Hum. Mutat.* 11: 456-460, 1998.  
PubMed ID : [9603438](#)
19. Daniels, M.; Shohat, T.; Brenner-Ullman, A.; Shohat, M. :  
**Familial Mediterranean fever: high gene frequency among the non-Ashkenazic and Ashkenazic Jewish populations in Israel.** *Am. J. Med. Genet.* 55: 311-314, 1995.  
PubMed ID : [7726228](#)
20. Dewalle, M.; Domingo, C.; Rozenbaum, M.; Ben-Chetrit, E.; Cattan, D.; Bernot, A.; Dross, C.; Dupont, M.; Notarnicola, C.; Levy, M.; Rosner, I.; Demaille, J.; Touitou, I. :  
**Phenotype-genotype correlation in Jewish patients suffering from familial Mediterranean fever (FMF).** *Europ. J. Hum. Genet.* 6: 95-97, 1998.
21. Dinarello, C. A.; Wolff, S. M.; Goldfinger, S. E.; Dale, D. C.; Alling, D. W. :  
**Colchicine therapy for familial Mediterranean fever: a double-blind trial.** *New Eng. J. Med.* 291: 934-937, 1974.  
PubMed ID : [4606353](#)
22. Dormer, A. E.; Hale, J. F. :  
**Familial Mediterranean fever, a cause of periodic fever.** *Brit. Med. J.* 1: 87-89, 1962.
23. Dupont, M.; Dross, C.; Smaoui, N.; Nedelec, B.; Grateau, G.; Clepet, C.; Gourdier, I. :

- Kone-Paut, I.; Delmonte, M.; Demaille, J.; Touitou, I.: Genetic diagnosis of familial Mediterranean fever. (FMF) using new microsatellite markers: example of two extensive non-Ashkenazi Jewish pedigrees. *J. Med. Genet.* 34: 375-381, 1997.  
PubMed ID : [9152834](#)
24. Ehrenfeld, E. N.; Eliakim, M.; Rachmilewitz, M. :  
**Recurrent polyserositis (familial Mediterranean fever: periodic disease): a report of fifty-five cases.** *Am. J. Med.* 31: 107-123, 1961.
25. Eshel, G.; Zemer, D.; Bar-Yochai, A. :  
**Acute orchitis in familial Mediterranean fever.** *Ann. Intern. Med.* 109: 164-165, 1988.  
PubMed ID : [3382109](#)
26. Fischel-Ghodsian, N.; Bu, X.; Oztas, S.; Prezant, T. R.; Danon, Y.; Shohat, T.; Rotter, J. I.; Shohat, M. :  
**The gene for familial Mediterranean fever maps to the short arm of chromosome 16 in both Armenians and non-Ashkenazi Jews.** (Abstract) *Am. J. Hum. Genet.* 51 (suppl.): A187, 1992.
27. Fischel-Ghodsian, N.; Bu, X.; Prezant, T. R.; Oeztas, S.; Huang, Z.-S.; Bohlman, M. C.; Rotter, J. I.; Shohat, M. :  
**Regional mapping of the gene for familial Mediterranean fever on human chromosome 16p13.** *Am. J. Med. Genet.* 46: 689-693, 1993.  
PubMed ID : [8362911](#)
28. Flatau, E.; Kohn, D.; Schiller, D.; Lurie, M.; Levy, E. :  
**Schonlein-Henoch syndrome in patients with familial Mediterranean fever.** *Arthritis Rheum.* 25: 42-47, 1982.  
PubMed ID : [7066036](#)
29. French FMF Consortium :  
**A candidate gene for familial Mediterranean fever.** *Nature Genet.* 17: 25-31, 1997.  
PubMed ID : [9288094](#)
30. French FMF Consortium :  
**Localization of the familial Mediterranean fever gene (FMF) to a 250-kb interval in non-Ashkenazi Jewish founder haplotypes.** *Am. J. Hum. Genet.* 59: 603-612, 1996.  
PubMed ID : [8751861](#)
31. Goldfinger, S. E. :  
**Colchicine for familial Mediterranean fever.** (Letter) *New Eng. J. Med.* 287: 1302, 1972.  
PubMed ID : [4636899](#)
32. Gruberg, L.; Aksentijevich, I.; Balow, J.; Dean, M.; Kovo, M.; Pras, M.; Kastner, D. L. :  
**Exclusion of candidate genes in familial Mediterranean fever.** (Abstract) *Cytogenet. Cell Genet.* 58: 2113, 1991.
33. Heller, H.; Sohar, E.; Gafni, J.; Heller, J. :  
**Amyloidosis in familial Mediterranean fever.** *Arch. Intern. Med.* 107: 539-550, 1961.
34. Hurwich, B. J.; Schwartz, J.; Goldfarb, S. :  
**Record survival of siblings with familial Mediterranean fever, phenotypes 1 and 2: case of renal vein thrombosis complicating the amyloidosis (phenotype 2).** *Arch. Intern. Med.* 125: 308-311, 1970.  
PubMed ID : [5412021](#)

35. Ilfeld, D.; Kuperman, O. :  
**Correction of a suppressor cell deficiency in four patients with familial Mediterranean fever by in vitro or in vivo colchicine.** *Clin. Exp. Immun.* 50: 99-106, 1982.
36. International FMF Consortium :  
**Ancient missense mutations in a new member of the RoRet gene family are likely to cause familial Mediterranean fever.** *Cell* 90: 797-807, 1997.  
PubMed ID : [9288758](#)
37. Janeway, T. C.; Mosenthal, H. O. :  
**An unusual paroxysmal syndrome, probably allied to recurrent vomiting, with a study of the nitrogen metabolism.** *Trans. Assoc. Am. Phys.* 23: 504-518, 1908.
38. Jones, M. B.; Adams, J. M.; Passer, J. A. :  
**Amyloidosis in a renal allograft in familial Mediterranean fever.** *Ann. Intern. Med.* 87: 579-581, 1977.  
PubMed ID : [335941](#)
39. Kastner, D. L.; Aksentijevich, I.; Gruberg, L.; Balow, J.; Dean, M.; Hampsch, K.; Gazit, E.; Kovo, M.; Pras, M. :  
**Familial Mediterranean fever: a 90 marker exclusion map and evidence for linkage to chromosome 17.** (Abstract) *Cytogenet. Cell Genet.* 58: 2115, 1991.
40. Kees, S.; Langevitz, P.; Zemer, D.; Padeh, S.; Pras, M.; Livneh, A. :  
**Attacks of pericarditis as a manifestation of familial Mediterranean fever (FMF).** *Quart. J. Med.* 90: 643-647, 1997.
41. Khachadurian, A. K.; Armenian, H. K. :  
**Familial paroxysmal polyserositis (familial Mediterranean fever): incidence of amyloidosis and mode of inheritance.** *Birth Defects Orig. Art. Ser.* X(4): 62-66, 1974.
42. Knecht, A.; de Beer, F. C.; Pras, M. :  
**Serum amyloid A protein in familial Mediterranean fever.** *Ann. Intern. Med.* 102: 71-72, 1985.  
PubMed ID : [3966749](#)
43. Lawrence, J. S.; Mellinkoff, S. M. :  
**Familial Mediterranean fever.** *Trans. Assoc. Am. Phys.* 72: 111-121, 1959.
44. Levy, E. N.; Shen, Y.; Kupelian, A.; Kruglyak, L.; Aksentijevich, I.; Pras, E.; Balow, J. E., Jr.; Linzer, B.; Chen, X.; Shelton, D. A.; Gumucio, D.; Pras, M.; Shohat, M.; Rotter, J. I.; Fischel-Ghodsian, N.; Richards, R. I.; Kastner, D. L. :  
**Linkage disequilibrium mapping places the gene causing familial Mediterranean fever close to D16S246.** *Am. J. Hum. Genet.* 58: 523-534, 1996.  
PubMed ID : [8644712](#)
45. Ludomirsky, A.; Passwell, J.; Boichis, H. :  
**Amyloidosis in children with familial Mediterranean fever.** *Arch. Dis. Child.* 56: 464-467, 1981.  
PubMed ID : [7259278](#)
46. Majeed, H. A.; Barakat, M. :  
**Familial Mediterranean fever (recurrent hereditary polyserositis) in children: analysis of 88 cases.** *Europ. J. Pediat.* 148: 636-641, 1989.

47. Matzner, Y.; Brzezinski, A. :  
**C5a-inhibitor deficiency in peritoneal fluids from patients with familial Mediterranean fever.**  
*New Eng. J. Med.* 311: 287-290, 1984.  
PubMed ID : [6738641](#)
48. Matzner, Y.; Partridge, R. E. H.; Levy, M.; Babior, B. M. :  
**Diminished activity of a chemotactic inhibitor in synovial fluids from patients with familial Mediterranean fever.**  
*Blood* 63: 629-633, 1984.  
PubMed ID : [6365203](#)
49. Meyerhoff, J. : Personal Communication. Salt Lake City, Utah and Baltimore, Md., 1978.
50. Meyerhoff, J. :  
**Familial Mediterranean fever: report of a large family, review of the literature, and discussion of the frequency of amyloidosis.**  
*Medicine* 59: 66-77, 1980.  
PubMed ID : [6986010](#)
51. Mollaret, P. :  
**La meningite endothelio-leucocytaire multi-recurrente benign: syndrome nouveau du maladie nouvelle?**  
*Bull. Soc. Med. Hop. Paris* 60: 121-122, 1944.
52. Ozdemir, A. I.; Sokmen, C. :  
**Familial Mediterranean fever among the Turkish people.**  
*Am. J. Gastroenterol.* 51: 311-316, 1969.  
PubMed ID : [5794010](#)
53. Ozyilkan, E.; Simsek, H.; Telatar, H. :  
**Absence of asthma in patients with familial Mediterranean fever.**  
*Israel J. Med. Sci.* 30: 237-238, 1994.  
PubMed ID : [8181925](#)
54. Pras, E.; Aksentijevich, I.; Gruberg, L.; Balow, J. E., Jr.; Prosen, L.; Dean, M.; Steinberg, A. D.; Pras, M.; Kastner, D. L. :  
**Mapping of a gene causing familial Mediterranean fever to the short arm of chromosome 16.**  
*New Eng. J. Med.* 326: 1509-1513, 1992.  
PubMed ID : [1579134](#)
55. Pras, E.; Aksentijevich, I.; Gruberg, L.; Shen, Y.; Prosen, L.; Balow, J. E., Jr.; Richards, R. I.; Pras, M.; Kastner, D. L. :  
**Locus homogeneity in familial Mediterranean fever.** (Abstract) *Am. J. Hum. Genet.* 51 (suppl.): A371, 1992.
56. Pras, E.; Aksentijevich, I.; Levy, E.; Gruberg, L.; Prosen, L.; Dean, M.; Pras, M.; Kastner, D. L. :  
**The gene causing familial Mediterranean fever maps to the short arm of chromosome 16 in Druze and Moslem Arab families.**  
*Hum. Genet.* 94: 576-577, 1994.  
PubMed ID : [7959700](#)
57. Pras, E.; Livneh, A.; Balow, J. E., Jr.; Pras, E.; Kastner, D. L.; Pras, M.; Langevitz, P. :  
**Clinical differences between North African and Iraqi Jews with familial Mediterranean fever.**  
*Am. J. Med. Genet.* 75: 216-219, 1998.  
PubMed ID : [9450890](#)
58. Pras, M.; Bronshpigel, N.; Zemer, D.; Gafni, J. :

- Variable incidence of amyloidosis in familial Mediterranean fever among different ethnic groups.**  
*Johns Hopkins Med. J.* 150: 22-26, 1982.  
PubMed ID : [7054581](#)

59. Ravid, M.; Robson, M.; Kedar, I. :  
**Prolonged colchicine treatment in four patients with amyloidosis.** *Ann. Intern. Med.* 87: 568-570, 1977.  
PubMed ID : [921085](#)

60. Rawashdeh, M. O.; Majeed, H. A. :  
**Familial Mediterranean fever in Arab children: the high prevalence and gene frequency.** *Europ. J. Pediat.* 155: 540-544, 1996.

61. Reich, C. B.; Franklin, E. C. :  
**Familial Mediterranean fever in an Italian family.** *Arch. Intern. Med.* 125: 337-340, 1970.  
PubMed ID : [5412026](#)

62. Reimann, H. A.; Moadie, J.; Semerdjian, S.; Sahyoun, P. F. :  
**Periodic peritonitis--heredity and pathology: report of seventy-two cases.** *J.A.M.A.* 154: 1254-1259, 1954.

63. Rogers, D. B.; Shohat, M.; Petersen, G. M.; Bickal, J.; Congleton, J.; Schwabe, A. D.; Rotter, J. I. :  
**Familial Mediterranean fever in Armenians: autosomal recessive inheritance with high gene frequency.** *Am. J. Med. Genet.* 34: 168-172, 1989.  
PubMed ID : [2816993](#)

64. Rubinger, D.; Friedlaender, M. M.; Popovtzer, M. M. :  
**Amelioration of familial Mediterranean fever during hemodialysis.** *New Eng. J. Med.* 301: 142-144, 1979.  
PubMed ID : [377075](#)

65. Saatci, U.; Ozen, S.; Ozdemir, S.; Bakkaloglu, A.; Besbas, N.; Topaloglu, R.; Arslan, S. :  
**Familial Mediterranean fever in children: report of a large series and discussion of the risk and prognostic factors of amyloidosis.** *Europ. J. Pediat.* 156: 619-623, 1997.

66. Sack, G. H., Jr. :  
**Serum amyloid A (SAA) gene variations in familial Mediterranean fever.** *Molec. Biol. Med.* 5: 61-67, 1988.  
PubMed ID : [2899833](#)

67. Sack, G. H., Jr.; Talbot, C. C., Jr.; McCarthy, B. G.; Harris, E. L.; Kastner, D.; Gruberg, L.; Pras, M. :  
**Exclusion of linkage between familial Mediterranean fever and the human serum amyloid A (SAA) gene cluster.** *Hum. Genet.* 87: 506-508, 1991.  
PubMed ID : [1679035](#)

68. Schlesinger, M.; Ilfeld, D. N.; Zamir, R.; Brautbar, C. :  
**Familial Mediterranean fever: no linkage with HLA.** *Tissue Antigens* 24: 65-66, 1984.  
PubMed ID : [6484932](#)

69. Schwabe, A. D.; Lehman, T. J. A. :  
**C5a-inhibitor deficiency—a role in familial Mediterranean fever? (Editorial)** *New Eng. J. Med.* 311: 325-326, 1984.  
PubMed ID : [6738643](#)

70. Schwabe, A. D.; Monroe, J. B. :  
**Meningitis in familial Mediterranean fever.** *Am. J. Med.* 85: 715-717, 1988.  
PubMed ID : [3055980](#)

71. Schwabe, A. D.; Nishizawa, A. :  
**Recurrent polyserositis (familial Mediterranean fever) in a Japanese.** *Jpn. J. Med.* 26: 370-372, 1987.  
PubMed ID : [3694919](#)

72. Schwabe, A. D.; Peters, R. S. :  
**Familial Mediterranean fever in Armenians: analysis of 100 cases.** *Medicine* 53: 453-462, 1974.  
PubMed ID : [4437392](#)

73. Schwabe, A. D.; Terasaki, P. I.; Barnett, E. V.; Territo, M. C.; Klinenberg, J. R.; Peters, R. S. :  
**Familial Mediterranean fever--recent advances in pathogenesis and management.** *West. J. Med.* 127: 15-23, 1977.

74. Shohat, M.; Bu, X.; Shohat, T.; Fischel-Ghodsian, N.; Magal, N.; Nakamura, Y.; Schwabe, A. D.; Schlesinger, M.; Danon, Y.; Rotter, J. I. :  
**The gene for familial Mediterranean fever in both Armenians and non-Ashkenazi Jews is linked to the alpha-globin complex on 16p: evidence for locus homogeneity.** *Am. J. Hum. Genet.* 51: 1349-1354, 1992.  
PubMed ID : [1463015](#)

75. Shohat, M.; Korenberg, J. R.; Schlesinger, M.; Shohat, T.; Petersen, G. M.; Schwabe, A.; Rotter, J. I. :  
**The gene for serum amyloid P component (APCS) is not a genetic marker for amyloidosis in familial Mediterranean fever.** (Abstract) *Cytogenet. Cell Genet.* 51: 1079, 1989.

76. Shohat, M.; Korenberg, J. R.; Schwabe, A. D.; Rotter, J. I. :  
**Hypothesis: familial Mediterranean fever--a genetic disorder of the lipocortin family?** *Am. J. Med. Genet.* 34: 163-167, 1989.  
PubMed ID : [2530899](#)

77. Shohat, M.; Korenberg, J. R.; Shohat, T.; Sack, G.; Schwabe, A.; Rotter, J. I. :  
**Serum amyloid A (SAA) locus is not associated with familial Mediterranean fever (FMF) or FMF-amyloidosis.** (Abstract) *Cytogenet. Cell Genet.* 51: 1079, 1989.

78. Shohat, M.; Livneh, A.; Zemer, D.; Pras, M.; Sohar, E. :  
**Twin studies in familial Mediterranean fever.** *Am. J. Med. Genet.* 44: 179-182, 1992.  
PubMed ID : [1456288](#)

79. Shohat, M.; Shohat, T.; Rotter, J. I.; Schlesinger, M.; Petersen, G. M.; Pribyl, T.; Sack, G.; Schwabe, A. D.; Korenberg, J. R. :  
**Serum amyloid A and P protein genes in familial Mediterranean fever.** *Genomics* 8: 83-89, 1990.  
PubMed ID : [1981994](#)

80. Shohat, T.; Shohat, M.; Petersen, G. M.; Sparkes, R. S.; Langfield, D.; Bickal, J.; Korenberg, J. R.; Schwabe, A. D.; Rotter, J. I. :  
**Genetic marker family studies in familial Mediterranean fever (FMF) in Armenians.** *Clin. Genet.* 38: 332-339, 1990.  
PubMed ID : [2282713](#)

81. Shohat, T.; Shohat, M.; ...n, D. B.; Wang, S. J.; Sparkes, R. S.; Soebabe, A. D.; Rotter, J. I. :  
**Familial Mediterranean fever--linkage studies with genetic markers on chromosome 6.** *Tissue Antigens* 36: 103-107, 1990.  
PubMed ID : [2278043](#)
82. Siegal, S. :  
**Familial paroxysmal polyserositis: analysis of fifty cases.** *Am. J. Med.* 36: 893-918, 1964.
83. Siegal, S. :  
**Benign paroxysmal peritonitis.** *Ann. Intern. Med.* 23: 1-22, 1945.
84. Sohar, E.; Gafni, J.; Pras, M.; Heller, H. :  
**Familial Mediterranean fever: a survey of 470 cases and review of literature.** *Am. J. Med.* 43: 227-253, 1967.  
PubMed ID : [5340644](#)
85. Sokmen, C. :  
**Comment.** *Trans. Assoc. Am. Phys.* 72: 120-121, 1959.
86. Sood, R.; Blake, T.; Aksentijevich, I.; Wood, G.; Chen, X.; Gardner, D.; Shelton, D. A.; Mangelsdorf, M.; Orsborn, A.; Pras, E.; Balow, J. E. Jr.; Centola, M. {and 16 others} :  
**Construction of a 1-Mb restriction-mapped cosmid contig containing the candidate region for the familial Mediterranean fever locus (MEFV) on chromosome 16p13.3.** *Genomics* 42: 83-95, 1997.  
PubMed ID : [9177779](#)
87. Wolff, S. M.; Dinarello, C. A.; Dale, D. C.; Goldfinger, S. E.; Alling, D. W. :  
**Colchicine therapy of familial Mediterranean fever.** (Abstract) *Clin. Res.* 22: 567A, 1974.
88. Yuval, Y.; Hemo-Zisser, M.; Zemer, D.; Sohar, E.; Pras, M. :  
**Dominant inheritance in two families with familial Mediterranean fever (FMF).** *Am. J. Med. Genet.* 57: 455-457, 1995.  
PubMed ID : [7677151](#)
89. Zemer, D.; Livneh, A.; Pras, M.; Sohar, E. :  
**Familial Mediterranean fever in the colchicine era: the fate of one family.** *Am. J. Med. Genet.* 45: 340-344, 1993.  
PubMed ID : [8434621](#)
90. Zemer, D.; Pras, M.; Sohar, E.; Modan, M.; Cabili, S.; Gafni, J. :  
**Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever.** *New Eng. J. Med.* 314: 1001-1005, 1986.  
PubMed ID : [3515182](#)
91. Zemer, D.; Revach, M.; Pras, M.; Modan, B.; Schor, S.; Sohar, E.; Gafni, J. :  
**A controlled trial of colchicine in preventing attacks of familial Mediterranean fever.** *New Eng. J. Med.* 291: 932-934, 1974.  
PubMed ID : [4606109](#)

## CLINICAL SYNOPSIS

[View Clinical Synopsis Entry](#)

### CONTRIBUTORS

Victor A. McKusick - updated : 10/9/1998  
Victor A. McKusick - updated : 9/9/1998  
Victor A. McKusick - updated : 4/30/1998  
Victor A. McKusick - updated : 2/19/1998  
Michael J. Wright - updated : 12/18/1997  
Victor A. McKusick - updated : 12/2/1997  
Victor A. McKusick - updated : 10/9/1997  
Michael J. Wright - updated : 10/2/1997  
Victor A. McKusick - updated : 8/21/1997  
Cynthia K. Ewing - updated : 2/25/1997  
Cynthia K. Ewing - updated : 11/14/1996

### CREATION DATE

Victor A. McKusick : 6/4/1986

### EDIT HISTORY

alopez : 10/28/1998  
terry : 10/9/1998  
terry : 10/7/1998  
terry : 10/1/1998  
alopez : 9/10/1998  
terry : 9/9/1998  
carol : 5/2/1998  
terry : 4/30/1998  
mark : 2/26/1998  
terry : 2/19/1998  
alopez : 1/15/1998  
terry : 12/18/1997  
mark : 12/8/1997  
terry : 12/2/1997  
terry : 12/1/1997  
alopez : 11/19/1997  
alopez : 11/12/1997  
alopez : 11/12/1997  
mark : 10/16/1997  
terry : 10/9/1997  
dholmes : 9/17/1997  
mark : 8/22/1997  
mark : 8/22/1997  
terry : 8/22/1997  
mark : 8/21/1997  
mark : 8/21/1997  
mark : 8/21/1997  
terry : 8/20/1997

mark : 7/16/1997  
lopez : 6/11/1997  
mark : 2/25/1997  
mark : 2/25/1997  
jamie : 2/5/1997  
jamie : 11/14/1996  
terry : 11/13/1996  
terry : 10/9/1996  
terry : 9/25/1996  
mark : 3/6/1996  
terry : 3/5/1996  
terry : 8/4/1995  
mark : 7/16/1995  
pfoster : 5/23/1995  
carol : 1/11/1995  
jason : 6/22/1994  
davew : 6/3/1994

#### ALLELIC VARIANTS

- 0001 : FAMILIAL MEDITERRANEAN FEVER
  - Mutation : MEFV, MET694VAL
- 0002 : FAMILIAL MEDITERRANEAN FEVER
  - Mutation : MEFV, MET694ILE
- 0003 : FAMILIAL MEDITERRANEAN FEVER
  - Mutation : MEFV, VAL726ALA
- 0004 : FAMILIAL MEDITERRANEAN FEVER
  - Mutation : MEFV, MET680ILE
- 0005 : FAMILIAL MEDITERRANEAN FEVER
  - Mutation : MEFV, GLU148GLN
- 0006 : FAMILIAL MEDITERRANEAN FEVER
  - Mutation : MEFV, GLU167ASP
- 0007 : FAMILIAL MEDITERRANEAN FEVER
  - Mutation : MEFV, THR267ILE
- 0008 : FAMILIAL MEDITERRANEAN FEVER
  - Mutation : MEFV, PHE479LEU
- 0009 : FAMILIAL MEDITERRANEAN FEVER
  - Mutation : MEFV, ILE692DEL
- 0010 : FAMILIAL MEDITERRANEAN FEVER
  - Mutation : MEFV, LYS695ARG
- 0011 : FAMILIAL MEDITERRANEAN FEVER
  - Mutation : MEFV, ALA744SER
- 0012 : FAMILIAL MEDITERRANEAN FEVER
  - Mutation : MEFV, ARG761HIS